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14. ABSTRACT
Neurological soft signs (NSS) are subtle indicators of brain dysfunction. NSS have been found to be elevated in a variety of mental disorders, including post-traumatic stress disorder (PTSD), but they have scarcely been studied in TBI. The present study measured NSS in the acute aftermath of a mTBI and evaluated their ability to predict subsequent postconcussive symptoms. We have finished all study recruitment, enrollment, and data analysis. We screened 99 subjects via the Massachusetts General Hospital Emergency Department leading to 21 viable subjects that were enrolled, three of whom were subsequently excluded for not meeting eligibility criteria. One additional subject was lost to follow-up after completion of the first visit. The remaining 17 enrolled subjects have successfully completed the full three-month protocol. The video-recorded data for all subjects was encrypted and analyzed by our off site consultant, Dr. Gurvits, the originator of the NSS battery in current use. A manuscript has been prepared and awaits submission.

15. SUBJECT TERMS- PTSD; Postconcussive Syndrome; Neurological Soft Signs.

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1. INTRODUCTION

Neurological soft signs (NSS) are subtle indicators of brain dysfunction. NSS have been found to be elevated in a variety of mental disorders, including post-traumatic stress disorder (PTSD), but they have scarcely been studied in TBI. The present study measured NSS in the acute aftermath of a mTBI and evaluated the ability of NSS to predict subsequent postconcussive symptoms.

2. KEYWORDS

Mild traumatic brain injury, concussion, neurocognitive disorder, post-concussive syndrome; neurological soft signs.

3. OVERALL PROJECT SUMMARY

Human subjects approvals were obtained from the Partners Health Care System and the Spaulding Rehabilitation Hospital Institutional Review Boards (IRBs) and the Department of Defense IRB. The performance and recording of the neurological soft signs (NSS) examination was rehearsed, and all necessary questionnaires and instruments were collected. Methods of encryption and safe transport of the video-recorded data to off-site consultant Dr. Gurvits, the originator of the NSS battery in current use, were developed and rehearsed. Recruitment strategies were developed and implemented in the Emergency Department at the Massachusetts General Hospital (MGH ED). Subject screening and enrollment began in September of the 01 year (month 4). 99 subjects were screened MGH ED leading to 21 viable subjects that were enrolled. Four subjects were subsequently excluded. The remaining 17 enrolled subjects successfully completed all three study visits (96-hour post-mTBI, 1-month post-mTBI, and 3-month post-mTBI) including neuropsychological testing and questionnaires. All video-recorded data was encrypted and scored by our off site consultant, Dr. Gurvits, the originator of the NSS battery in current use, and subsequently analyzed. We received a no-cost extension from May 20 to November 19 in order to complete and sufficiently analyze our original enrollment targets. A manuscript is currently in preparation.

Group mean average NSS scores at the three assessment periods are shown in Figure A. As predicted, these scores were elevated at Visit 1. They declined at Visit 2 and stabilized at Visit 3 ($F(2,32)=20.3$, $p<0.001$). A similar pattern was seen for the average of the six most impaired signs (the NSS-6). Group mean scores on the Beck Depression Inventory (BDI) are also shown in Figure 1. In contrast to the average NSS scores, BDI scores did not show an overall decline over time, with a drop-off in score seen only at Visit 3. See Table A. in the Appendix for a Spearman rho correlation matrix of all variables. Contrary to prediction, the average NSS-45 score at Visit 1 did not significantly predict any of the four key outcome measures at Visit 3, viz., self-reported post-concussive symptoms on the BC-PSI or RPQ, functional impairment on the MPAI-4, or overall neuropsychological impairment (NCI), (all ρ's ≤ 0.39, n.s.). Neither did Visit 1 BESS scores significantly predict any of the key four outcome measures (all ρ's $\leq$

0.39, n.s.). The correlations between avgNSS-45 at Visit 1 and BESS scores at Visit 3 were high (ρ=0.65, $p<0.01$); indeed these two measures inter-correlated highly at each visit (all ρ's ≥ 0.55, $p<0.05$), suggesting that the NSS battery and BESS reflected a common underlying functional neurological domain. However, when the subset of NSS measures that were elevated beyond the mild range (≥1.5/3) at Visit one (avgNSS-6) were correlated to Visit 3 outcome measures, significant associations emerged for the BC-PSI and RPQ but not for the MPAI-4 or NCI. When the 4 factors underlying the RPQ were analyzed separately, it was clear that relationship between avgNSS-6 at Visit 1 and overall RPQ at Visit 3 was driven primarily by the cognitive factor (RPQ-C, ρ=0.57, $p<0.05$).

In contrast to the only partially significant predictions of outcome obtained with the NSS measures, the BDI-II was consistently associated with outcome, with moderate effect sizes obtained on all four measures (all ρ's≥ 0.52, $p<0.05$). A parallel pattern was seen with PCL-17 at Visit 1 as the predictor of outcome (all ρ's≥ 0.48, $p<0.05$). The correlations between BDI-II and PCL were very high at each visit (all ρ's≥ 0.77), suggesting that these instruments reflected a common underlying psychopathological domain.

4. KEY RESEARCH ACCOMPLISHMENTS

- Employed an aggressive recruitment strategy to successfully obtain key clinical indices in the very acute period (within 4 days post-injury) allowing for the successful capture of a rapidly evolving phenomenon.
- Identified the most sensitive NSS signs (e.g. heel-walking) which have potential for a bedside, on-field, or battlefield assessment tool.
- Validated the finding in the existing literature that early affective markers are strong predictors of poor outcome in mTBI.

5. CONCLUSION

The findings of this pilot study add incrementally to the body of knowledge on factors that predispose head -injured individuals to poor outcome three months after incurring a mTBI. These and related findings could both inform screening strategies designed to identify at-risk civilians and Service members prior to injury occurrence, in addition to developing reliable and practical tools for symptom monitoring that could inform return to play/work/duty decisions. A manuscript is in the final stages of preparation for submission to a peer-reviewed journal.

6. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:

a. Greenberg, MS; Wood, NW; Spring JD; Gurvits TV; Nagurney JT; Zafonte, R; Pitman RK. Neurological Soft Signs and Psychological and Postconcussive Symptoms during Recovery from Mild Traumatic Brain Injury, *in preparation.*

b. Poster Presentation and Abstract Publication at Society of Biological Psychiatry 68th Annual Scientific Convention, May 16-18, 2013, in San Francisco, CA:

Greenberg MS, Wood NE, Spring JD, Nagurney JT, Zafonte RD, Gurvits TV, Pitman RK. Neurological soft signs in mild traumatic brain injury. *Biological Psychiatry* 2013:73: 208S.

7. INVENTIONS, PATENTS AND LICENSES

Nothing to Report

8. REPORTABLE OUTCOMES

Nothing to Report

9. OTHER ACHIEVEMENTS

Nothing to Report

10. REFERENCES

Nothing to Report

11. APPENDICES

List of Study Personnel

Nagurney, John - Co-I
Parry, Blair – ED Supervisor
Zink Thielker, Korie -Screener
Callahan, Ryan - Screener
Danh, Sandy - Screener
Hansen, Paul - Screener
Howell, Melissa - Screener
Mooncai, Theodore - Screener
Rubin, John - Screener
Pruzansky, Alix - Screener
Zafonte, Ross – Co-I
Frazier, Judith - Coordinator
Purohit, Maulik - Co-I
Pitman, Roger – PI
Greenberg, Mark - Co-I
Spring, Justin - RA
Wood, Nellie – RA

FIGURE A

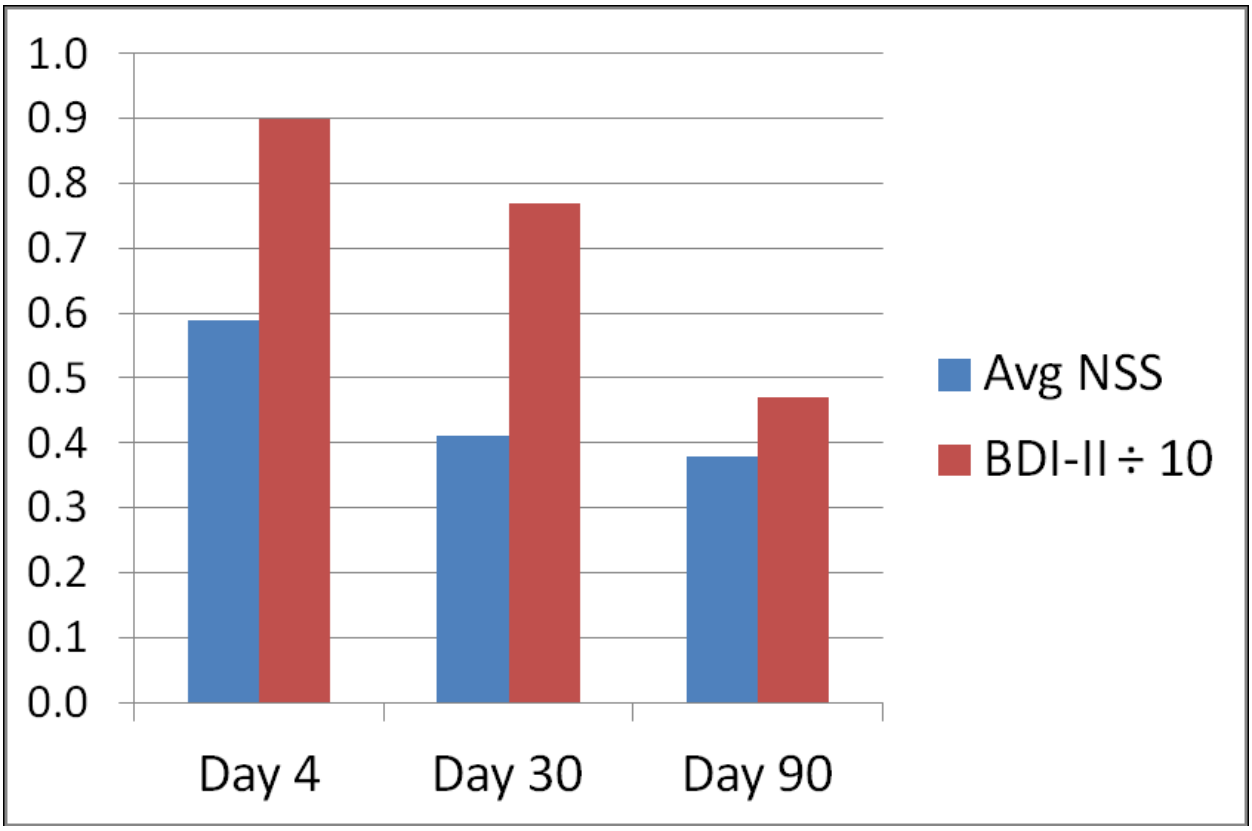

TABLE A

Spearman's rho Correlations

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	AA	BB	CC	DD	EE	FF	GG	HH	II	JJ	KK	LL
A NSS_AVG_A	1.000	.831**	-.111	.024	.067	.299	.005	-.348	-.032	-.171	.699**	.706**	.522*	.351	.407	.411	.462	.337	.304	.009	.047	.740**	.314	.430	.271	.378	.385	.193	.465	.172	-.143	.255	.189	.648**	.181	.185	.158	-.160
B NSS_AVG_BIG_6_A	.831**	1.000	-.055	-.012	-.157	.186	.073	-.125	.125	-.002	.598*	.610**	.684**	.359	.426	.382	.558*	.350	.347	.134	.201	.446	.342	.292	.330	.516*	.540*	.334	.569*	.216	.064	.444	.390	.504*	.346	.332	.191	.084
C BC_PSI_A	-.111	-.055	1.000	.774**	.384	.353	.613**	.650**	.400	.472	-.054	.032	-.086	.290	.190	-.149	.260	.526*	.138	.307	.400	.026	.396	.263	.329	-.009	.156	.155	.070	.372	.009	-.014	.171	.065	.079	-.026	.348	.436
D RPQ_total_A	.024	-.012	.774**	1.000	.564*	.652**	.630**	.642**	.315	.401	.085	-.003	.004	.410	.256	-.034	.298	.566*	.273	.213	.325	.213	.379	.215	.343	.118	.245	.237	.138	.572*	.119	.019	.246	.329	.088	.066	.555*	.291
E RPQ_somatic_A	.067	-.157	.384	.564*	1.000	.214	.061	.104	-.033	-.065	.143	.181	.062	.064	-.043	-.150	.001	.142	-.132	-.273	-.067	.401	.096	.369	.149	-.294	-.176	.070	-.297	.104	-.247	-.199	-.256	.270	-.267	-.172	.095	-.010
F RPQ_cognitive_A	.299	.186	.353	.652**	.214	1.000	.183	.200	.168	.312	.419	.197	.077	.400	.563*	.430	.474	.516*	.574*	.208	.286	.312	.533*	.096	.171	.390	.539*	.372	.389	.623**	.328	.201	.506*	.593*	.408	.200	.621**	.123
G RPQ_emotional_A	.005	.073	.613**	.630**	.061	.183	1.000	.439	.273	.268	-.013	-.185	-.179	.230	.020	-.217	.005	.344	-.042	.282	.240	.026	.148	.062	.230	-.022	.080	.023	.117	.354	-.082	-.058	-.018	.048	-.065	-.041	.308	.266
H RPQ_visaud_A	-.348	-.125	.650**	.642**	.104	.200	.439	1.000	.301	.437	-.378	-.107	.030	.226	-.022	-.280	.096	.300	.104	.290	.271	-.378	.014	.091	.396	.107	.061	.088	-.040	.322	.332	-.043	.246	-.129	-.024	.041	.308	.302
I PCL_A	-.032	.125	.400	.315	-.033	.168	.273	.301	1.000	.819**	-.004	-.007	.173	.445	.469	.282	.531*	.569*	.351	.697**	.687**	-.227	.625**	.038	.062	.571*	.484*	.414	.419	.526*	.454	.712**	.547*	.220	.578*	.516*	.506*	.487*
J BDI_A_total	-.171	-.002	.472	.401	-.065	.312	.268	.437	.819**	1.000	-.231	-.169	-.132	.522*	.486*	.186	.529*	.656**	.500*	.766**	.816**	-.289	.625**	-.126	-.132	.554*	.520*	.486*	.361	.586*	.475	.601*	.521*	.078	.532*	.397	.586*	.578*
K BESS_9_grandtotal_A	.699**	.598*	-.054	.085	.143	.419	-.013	-.378	-.004	-.231	1.000	.709**	.456	.210	.442	.373	.372	.233	.073	-.072	.035	.724**	.402	.561*	.462	.137	.387	.205	.291	.008	-.086	.088	.148	.839**	.139	.066	-.016	.006
L NSS AVG B	.706**	.610**	.032	-.003	.181	.197	-.185	-.107	-.007	-.169	.709**	1.000	.653**	.152	.268	.248	.301	.189	-.012	-.118	-.005	.546*	.216	.788**	.567*	.165	.223	.109	.207	-.071	.028	.071	.099	.634**	.012	.026	-.111	.065
M NSS AVG BIG 6 B	.522*	.684**	-.086	.004	.062	.077	-.179	.030	.173	-.132	.456	.653**	1.000	.147	.180	.322	.352	.049	.083	-.151	.016	.239	.176	.469	.556*	.338	.273	.093	.383	.054	.273	.425	.337	.445	.288	.297	.016	-.019
N BC_PSI_B	.351	.359	.290	.410	.064	.400	.230	.226	.445	.522*	.210	.152	.147	1.000	.844**	.618**	.834**	.853**	.663**	.730**	.856**	.166	.799**	.213	.243	.672**	.774**	.757**	.630**	.664**	.394	.620**	.597*	.385	.579*	.635**	.664**	.084
O RPQ_total_B	.407	.426	.190	.256	-.043	.563*	.020	-.022	.469	.486*	.442	.268	.180	.844**	1.000	.843**	.919**	.849**	.769**	.723**	.772**	.183	.892**	.090	.074	.770**	.947**	.871**	.780**	.671**	.488*	.690**	.765**	.479	.745**	.748**	.671**	.215
P RPQ_somatic_B	.411	.382	-.149	-.034	-.150	.430	-.217	-.280	.282	.186	.373	.248	.322	.618**	.843**	1.000	.733**	.540*	.720**	.440	.480	.087	.678**	-.016	-.031	.776**	.800**	.729**	.804**	.604*	.542*	.735**	.760**	.308	.813**	.811**	.598*	.009
Q RPQ_cognitive_B	.462	.558*	.260	.298	.001	.474	.005	.096	.531*	.529*	.372	.301	.352	.834**	.919**	.733**	1.000	.857**	.757**	.668**	.773**	.219	.888**	.103	.162	.789**	.919**	.805**	.806**	.673**	.497*	.753**	.784**	.478	.733**	.775**	.687**	.227
R RPQ_emotional_B	.337	.350	.526*	.566*	.142	.516*	.344	.300	.569*	.656**	.233	.189	.049	.853**	.849**	.540*	.857**	1.000	.724**	.778**	.798**	.216	.818**	.121	.091	.690**	.824**	.778**	.702**	.722**	.336	.548*	.667**	.354	.557*	.633**	.719**	.441
S RPQ visaud B	.304	.347	.138	.273	-.132	.574*	-.042	.104	.351	.500*	.073	-.012	.083	.663**	.769**	.720**	.757**	.724**	1.000	.559*	.565*	.082	.618**	-.208	-.163	.861**	.781**	.681**	.744**	.706**	.360	.655**	.864**	.119	.811**	.653**	.725**	.283
T PCL B	.009	.134	.307	.213	-.273	.208	.282	.290	.697**	.766**	-.072	-.118	-.151	.730**	.723**	.440	.668**	.778**	.559*	1.000	.645**	-.285	.653**	-.176	-.136	.652**	.724**	.699**	.561*	.570*	.478	.597*	.576*	.089	.520*	.635**	.569*	.319
U BDI_B_total	.047	.201	.400	.325	-.067	.286	.240	.271	.687**	.816**	.035	-.005	.016	.856**	.772**	.480	.773**	.798**	.565*	.845**	1.000	-.106	.855**	.080	.090	.619**	.742**	.724**	.550*	.604*	.488*	.707**	.583*	.236	.644**	.581*	.600*	.366
V BESS_9_grandtotal_B	.740**	.446	.026	.213	.401	.312	.026	-.378	-.227	-.289	.724**	.546*	.239	.166	.183	.087	.219	.216	.082	-.285	-.106	1.000	.225	.533*	.298	-.054	.086	-.070	.133	-.102	-.502*	-.140	-.113	.637**	-.098	-.198	-.095	-.053
W MPAI4_total_B	.314	.342	.396	.379	.096	.533*	.148	.014	.625**	.625**	.402	.216	.176	.799**	.892**	.678**	.888**	.818**	.618**	.653**	.855**	.225	1.000	.191	.167	.620**	.823**	.723**	.676**	.662**	.438	.715**	.648**	.530*	.732**	.620**	.662**	.285
X NSS_AVG_C	.430	.292	.263	.215	.369	.096	.062	.091	.038	-.126	.561*	.788**	.469	.213	.090	-.016	.103	.121	-.208	-.176	.080	.533*	.191	1.000	.806**	-.101	-.049	-.090	-.099	-.160	-.170	-.091	-.109	.552*	-.114	-.238	-.206	.041
Y NSS_AVG_BIG_6_C	.271	.330	.329	.343	.149	.171	.230	.396	.062	-.132	.462	.567*	.556*	.243	.074	-.031	.162	.091	-.163	-.136	.090	.298	.167	.806**	1.000	-.030	.035	-.088	-.003	.002	.085	-.050	.088	.498*	-.016	-.093	-.032	-.056
Z BC PSI C	.378	.516*	-.009	.118	-.294	.390	-.022	.107	.571*	.554*	.137	.165	.338	.672**	.770**	.776**	.789**	.690**	.861**	.652**	.619**	-.054	.620**	-.101	-.030	1.000	.837**	.717**	.840**	.721**	.592*	.854**	.912**	.211	.853**	.828**	.717**	.317
AA RPQ_total_C	.385	.540*	.156	.245	-.176	.539*	.080	.061	.484*	.520*	.387	.223	.273	.774**	.947**	.800**	.919**	.824**	.781**	.724**	.742**	.086	.823**	-.049	.035	.837**	1.000	.871**	.871**	.691**	.583*	.739**	.835**	.415	.765**	.808**	.688**	.321
BB RPQ_somatic_C	.193	.334	.155	.237	.070	.372	.023	.088	.414	.486*	.205	.109	.093	.757**	.871**	.729**	.805**	.778**	.681**	.699**	.724**	-.070	.723**	-.090	-.088	.717**	.871**	1.000	.638**	.708**	.545*	.651**	.689**	.225	.633**	.802**	.702**	.290
CC RPQ_cognitive_C	.465	.569*	.070	.138	-.297	.389	.117	-.040	.419	.361	.291	.207	.383	.630**	.780**	.804**	.806**	.702**	.744**	.561*	.550*	.133	.676**	-.099	-.003	.840**	.871**	.638**	1.000	.625**	.507*	.748**	.817**	.253	.771**	.827**	.618**	.284
DD RPQ_emotional_C	.172	.216	.372	.572*	.104	.623**	.354	.322	.526*	.586*	.008	-.071	.054	.664**	.671**	.604*	.673**	.722**	.706**	.570*	.604*	-.102	.662**	-.160	.002	.721**	.691**	.708**	.625**	1.000	.621**	.640**	.717**	.232	.670**	.713**	.994**	.190
EE RPQ_visaud_C	-.143	.064	.009	.119	-.247	.328	-.082	.332	.454	.475	-.086	.028	.273	.394	.488*	.542*	.497*	.336	.360	.478	.488*	-.502*	.438	-.170	.085	.592*	.583*	.545*	.507*	.621**	1.000	.605*	.640**	.148	.550*	.714**	.616**	.098
FF PCL C	.255	.444	-.014	.019	-.199	.201	-.058	-.043	.712**	.601*	.088	.071	.425	.620**	.690**	.735**	.753**	.548*	.655**	.597*	.707**	-.140	.715**	-.091	-.050	.854**	.739**	.651**	.748**	.640**	.605*	1.000	.767**	.210	.886**	.811**	.630**	.239
GG BDI C total	.189	.390	.171	.246	-.256	.506*	-.018	.246	.547*	.521*	.148	.099	.337	.597*	.765**	.760**	.784**	.667**	.864**	.576*	.583*	-.113	.648**	-.109	.088	.912**	.835**	.689**	.817**	.717**	.640**	.767**	1.000	.170	.900**	.800**	.717**	.394
HH BESS_9_grandtotal_C	.648**	.504*	.065	.329	.270	.593*	.048	-.129	.220	.078	.839**	.634**	.445	.385	.479	.308	.478	.354	.119	.089	.236	.637**	.530*	.552*	.498*	.211	.415	.225	.253	.232	.148	.210	.170	1.000	.146	.106	.222	-.100
II MPAI4_total_C	.181	.346	.079	.088	-.267	.408	-.065	-.024	.578*	.532*	.139	.012	.288	.579*	.745**	.813**	.733**	.557*	.811**	.520*	.644**	-.098	.732**	-.114	-.016	.853**	.765**	.633**	.771**	.670**	.550*	.886**	.900**	.146	1.000	.743**	.666**	.316
JJ ICD_CM_C	.185	.332	-.026	.066	-.172	.200	-.041	.041	.516*	.397	.066	.026	.297	.635**	.748**	.811**	.775**	.633**	.653**	.635**	.581*	-.198	.620**	-.238	-.093	.828**	.808**	.802**	.827**	.713**	.714**	.811**	.800**	.106	.743**	1.000	.717**	.158
KK DSM_IV_C	.158	.191	.348	.555*	.095	.621**	.308	.308	.506*	.586*	-.016	-.111	.016	.664**	.671**	.598*	.687**	.719**	.725**	.569*	.600*	-.095	.662**	-.206	-.032	.717**	.688**	.702**	.618**	.994**	.616**	.630**	.717**	.222	.666**	.717**	1.000	.157
LL NCI_C	-.160	.084	.436	.291	-.010	.123	.266	.302	.487*	.578*	.006	.065	-.019	.084	.215	.009	.227	.441	.283	.319	.366	-.053	.285	.041	-.056	.317	.321	.290	.284	.190	.098	.239	.394	-.100	.316	.158	.157	1.000

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).